HFA - 305 | Division of Dockets Management

Date of Approval: APR 21 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-833

IVOMEC Plus Injection for Cattle
(ivermectin and clorsulon)

To extend the period of persistent effect for *Oesophagostomum radiatum* from 14 to 28 days and for *Trichostrongylus axei* and *Cooperia punctata* from 14 to 21 days.

Sponsored by:
Merial Ltd.

1. GENERAL INFORMATION

a. File Number:	NADA 140-833
b. Sponsor:	Merial Ltd. 3239 Satellite Blvd., Bldg. 500, Duluth, GA 30096-4640 Drug Labeler Code: 050604
c. Established Name:	Ivermectin and clorsulon
d. Proprietary Name:	IVOMEC Plus Injection for Cattle
e. Dosage Form:	Sterile injectable solution
f. How Supplied:	50 mL rubber capped bottle, and 200, 500, and 1000 mL soft collapsible packs for use with an automatic syringe
g. How Dispensed:	Over-the-Counter (OTC)
h. Amount of Active Ingredients:	10 mg (1%) ivermectin and 100 mg (10%) clorsulon/mL
i. Route of Administration:	Subcutaneous
j. Species/Class:	Cattle
k. Recommended Dosage:	1 mL for each 50 kg (110 lb) of body weight, or 200 mcg ivermectin and 2 mg clorsulon per kg
l. Pharmacological Category:	Antiparasitic

m. Indications: For the effective treatment and control of the following parasites in cattle:

Gastrointestinal Roundworms (adults and fourth-stage larvae):
Ostertagia ostertagi (including inhibited *O. ostertagi*)
O. lyrata
Haemonchus placei
Trichostrongylus axei
T. colubriformis
Cooperia oncophora
C. punctata
C. pectinata
Bunostomum phlebotomum
Nematodirus helvetianus (adults only)
N. spathiger (adults only)
Oesophagostomum radiatum

Lungworms (adults and fourth-stage larvae):
Dictyocaulus viviparus

Liver Flukes:
Fasciola hepatica (adults only)

Cattle Grubs (parasitic stages):
Hypoderma bovis
H. lineatum

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites (cattle scab):
Psoroptes ovis (syn. *P. communis* var. bovis)
Sarcoptes scabiei var. *bovis*

Persistent Activity
IVOMEC Plus Injection has been proved to effectively control infections and to protect cattle from reinfection with: *Dictyocaulus viviparus* for 28 days after treatment; *Ostertagia ostertagi* for 21 days after treatment; and *Oesophagostomum radiatum, Haemonchus placei, Trichostrongylus axei, Cooperia punctata,* and *Cooperia oncophora* for 14 days after treatment.

n. Effect of Supplement: To extend the persistent effect periods for *Oesophagostomum radiatum* from 14 to 28 days after treatment and *Cooperia punctata* and *Trichostrongylus axei* from 14 to 21 days after treatment. At this time, the labeling is being revised to reflect updated environmental information and to add the veal calf warning statement to the residue information section.

2. *EFFECTIVENESS*

a. Dose Characterization

Effectiveness studies were presented in the original NADA 140-833 FOI Summary approval dated September 17, 1990, establishing the recommended effective dose of IVOMEC Plus Injection for the treatment and control of internal and external parasites.

b. Substantial Evidence for Persistent Effectiveness against Endoparasites

IVOMEC Plus Injection for Cattle is identical to IVOMEC Injection for Cattle except that it contains clorsulon. For the purposes of the therapeutic claims for the original approval of IVOMEC Plus dated September 17, 1990, effectiveness of clorsulon against *Fasciola hepatica* was demonstrated and noninterference of clorsulon with ivermectin was demonstrated. It was concluded that IVOMEC Injection and IVOMEC Plus were equivalent with regards to the effectiveness of ivermectin for treatment and control of various nematodes and ectoparasites. All the therapeutic claims for IVOMEC Injection were granted to IVOMEC Plus. Since these formulations are equivalent with regards to the effectiveness of ivermectin, it was decided that all the persistence claims granted to IVOMEC Injection could be granted to IVOMEC Plus with one persistent effect study conducted with IVOMEC Plus in a representative parasite species. In the original approval of IVOMEC Plus for persistent effect, studies were conducted in 6 of the 7 parasites approved for IVOMEC Injection.

Three studies (ASR 15065, 15110, and 15111) conducted to evaluate the persistent activity of IVOMEC Injection were previously evaluated using arithmetic means. Subsequent to the original review, the VICH guidance #90 "Effectiveness of Anthelmintics: General Recommendations VICH GL7" was finalized March 26, 2001. It allowed for the evaluation of parasite effectiveness studies using geometric means. For each study, the efficacy was determined by comparing the geometric mean worm counts of the treated groups with those of an untreated control group for each parasite species present in at least six adequately infected control animals. P-values were computed for each parasite species using contrasts in a one-way analysis of variance or unequal-variance t-tests on log-transformed counts, or using Wilcoxon's rank-sum test. The period of persistent activity was defined as the time during which the efficacy against a genus species was $\geq 90\%$.

For an indication to be granted, a minimum of two studies is required that have the following: an adequate level of infection in 6 control animals, a statistically significant difference between treated and control animals at $P<0.05$, and 90% efficacy using geometric means for each genus species of parasite and at each persistent effect period. If there are more than 2 studies, then the geometric means of the percent efficacy against a genus species of parasite from each study is added together and divided by the number of studies with that genus species of parasite. If this average is greater than or equal to 90%, then the claim may be granted. These three studies met the above criteria and were reevaluated using geometric means. The overall percent efficacies from three studies for *Trichostrongylus axei* and *Cooperia punctata* at 21 days are 93% and 90%, respectively. Two studies at 28 days for *Oesophagostomum radiatum* both demonstrated percent efficacy $\geq 90\%$. The

following are granted for IVOMEC Injection and IVOMEC Plus: To extend the persistent effect periods for *Oesophagostomum radiatum* from 14 to 28 days after treatment and *Cooperia punctata* and *Trichostrongylus axei* from 14 to 21 days after treatment. The three trials are individually summarized below.

B.1 Trial ASR 15065

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2) Investigator: Bruce N. Kunkle, D.V.M., M.S., Ph.D.
Merial Limited
Fulton, Missouri

3) General Design:

a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

b. Animals: Thirty (30) Holstein calves (10 per group), approximately 4 to 5 months old and weighing 157 to 234 kg at the start of the study were used. All animals were treated with another anthelmintic during the acclimation period to eliminate existing infections.

c. Treatment Groups: There were 3 treatment groups. The treated groups received IVOMEC Injection or IVOMEC Plus. The negative controls received no treatment.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: 1000 L_3 *Trichostrongylus axei* and *Cooperia* spp. Days 1 to 21 and 100 L_3 *Oesophagostomum radiatum* Days 1 to 28. There were larvae of other genus species given for various lengths of time that are not pertinent to this approval and are not reported.

e. Dosage Form: IVOMEC Injection, 10 mg ivermectin/mL and IVOMEC Plus, 10 mg ivermectin/mL and 100 mg clorsulon/mL.

f. Route of Administration: Subcutaneous

g. Dose: 1 mL/50 kg body weight for both formulations given once, 200 mcg ivermectin per kg for IVOMEC Injection or 200 mcg ivermectin and 2 mg clorsulon per kg for IVOMEC Plus.

h. Test Duration: 49 to 50 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 to 50 days after treatment, 28 to 29 days after the last *Trichostrongylus axei* and *Cooperia*

spp. larvae were administered and 21 to 22 days after the last *Oesophagostomum radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for the following two genus species. Only the results for the IVOMEC Injection group are reported as the extension of the persistent effect periods for IVOMEC Plus are based upon those proven for IVOMEC Injection. Efficacy is summarized in Table 2.1:

Table 2.1 Trial ASR 15065 - Percent Efficacy IVOMEC Injection 21-day Persistent Effect Period

Nematode Species	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Injection
Cooperia punctata	3169.8	67.9	98
Trichostrongylus axei	3826.9	83.3	98

5) Adverse Reactions: There were no adverse reactions in the IVOMEC Injection group. One animal in the IVOMEC Plus group died 22 days after treatment. The apparent cause of death was esophageal impaction, which was not believed to be related to the experimental treatment.

B.2 Trial ASR 15110

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2) Investigator: Edward G. Johnson, D.V.M.
Johnson Research
Parma, Idaho

3) General Design:

a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

b. Animals: Thirty (30) Holstein male calves (24 castrated and 6 intact), approximately 4 to 12 months old and weighing 130 to 186 kg at the start of the study were used. Animals were clear of patent infections at the time of treatment.

c. Treatment Groups: There were 3 treatment groups (10 animals per group). One group received IVOMEC Injection. The negative controls received no treatment. One group received a medication which is not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Cooperia punctata* (1000 per day for

21 days), *Trichostrongylus axei* (1000 per day for 21 days), and *Oesophagostomum radiatum* (100 per day for 28 days). There were larvae of other genus species given for various lengths of time that are not pertinent to this approval and are not reported.

e. Dosage Form: The dosage form was IVOMEC Injection, 10 mg ivermectin/mL.

f. Route of Administration: Subcutaneous

g. Dose: 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 days after treatment, 28 days after the last *Cooperia* spp. and *T. axei* larvae and 21 days after the last *O. radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for *C. punctata, T. axei,* and *O. radiatum.* Efficacy is summarized in Table 2.2:

Table 2.2 Trial ASR 15110 - Percent Efficacy IVOMEC Injection 21-day or 28-day persistent effect periods

Nematode Species	Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Injection
C. punctata	21	1470.7	374.4	75
T. axei	21	588.7	109.7	81
O. radiatum	28	278.8	24.0	91

5) Adverse Reactions: There were no adverse reactions to treatment.

B.3 Trial ASR 15111

1) Type of Study: Dose confirmation study in cattle with induced infections of gastrointestinal roundworms.

2) Investigator: Bruce N. Kunkle, D.V.M., M.S., Ph.D.
Merial Limited
Fulton, Missouri

3) General Design:

a. Purpose: To determine the period after treatment during which infections of gastrointestinal roundworms are controlled.

b. Animals: Thirty (30) Holstein heifer calves, approximately 5 to 6 months old and weighing 165 to 268 kg at the start of the study were used. Animals were free of patent infections at the time of infection.

c. Treatment Groups: There were 3 treatment groups (10 animals per group). One group received IVOMEC Injection. The negative controls received no treatment. One group received a medication which was not pertinent to this approval and is not reported.

d. Infection: Infective larvae were given to each animal daily, starting on the day of treatment, according to the following schedule: *Cooperia punctata* (1000 per day for 21 days), *Trichostrongylus axei* (1000 per day for 21 days), and *Oesophagostomum radiatum* (100 per day for 28 days). There were larvae of other genus species given for various lengths of time that were not pertinent to this approval and are not reported.

e. Dosage Form: The dosage form was IVOMEC Injection, 10 mg ivermectin/mL.

f. Route of Administration: Subcutaneous

g. Dose: 1 mL/50 kg body weight (200 mcg ivermectin/kg body weight) once.

h. Test Duration: 49 days after treatment.

i. Pertinent Variables Measured: Worm counts were determined at necropsy, 49 days after treatment, 28 days after the last *Cooperia* spp. and *T. axei* larvae and 21 days after the last *O. radiatum* larvae were administered.

4) Results: There was an adequate level of infection in at least 6 control animals for *C. punctata, T. axei,* and *O. radiatum.* Efficacy is summarized in Table 2.3:

Table 2.3 Trial ASR 15111 - Percent Efficacy IVOMEC Injection 21-day or 28-day persistent effect periods

Nematode Species	Persistent Effect Period	Geometric Mean in Controls	Geometric Mean in Treated	% Efficacy of IVOMEC Injection
C. punctata	21	2917.8	33.5	99
T. axei	21	2122.8	9.9	99
O. radiatum	28	174.2	2.0	99

5) Adverse Reactions: There were no adverse reactions to treatment.

3. TARGET ANIMAL SAFETY

No further target animal safety data were required from the original approval as discussed in the parent NADA 140-833 FOI Summary approval dated September 17, 1990.

4. HUMAN SAFETY

No further human food safety data were required from the original approval as discussed in the parent NADA 140-833 FOI summary approval dated September 17, 1990. There is a 49-day withdrawal period for slaughter, a withdrawal period for milk has not been established, and a withdrawal period has not been established for pre-ruminating calves.

5. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that IVOMEC Plus Injection for Cattle when administered once at 200 mcg ivermectin and 2 mg clorsulon/kg body weight is safe and effective for the extension of the following persistent effect periods: for *Oesophagostomum radiatum* from 14 to 28 days after treatment and *Cooperia punctata* and *Trichostrongylus axei* from 14 to 21 days after treatment.

The following has been added to the residue information section of the labeling, "A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal".

The Agency has concluded that this product may retain over-the-counter marketing status because adequate directions for use have been written for the layperson and the conditions of use prescribed on the label are likely to be followed in practice.

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did require a reevaluation of safety or effectiveness data in the parent application. Previously submitted studies were reevaluated using geometric means allowing the persistent effect period for 3 nematode species to be extended.

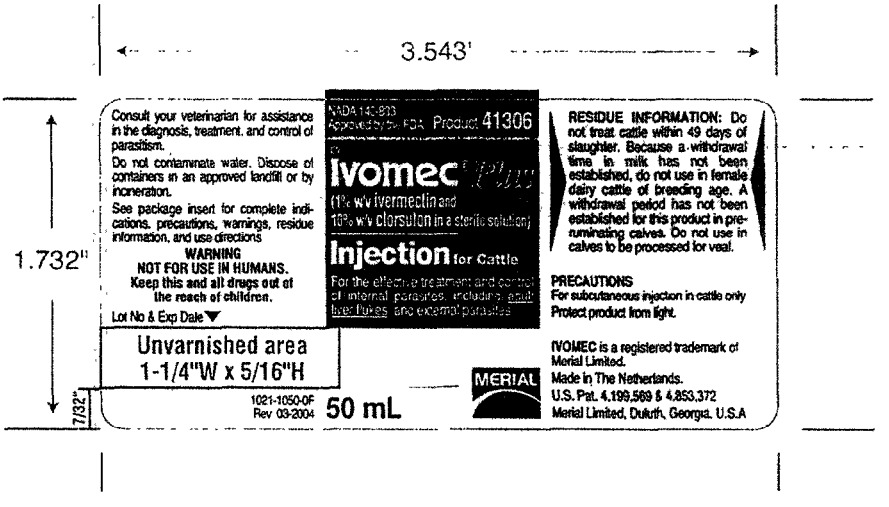
Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the extension of 3 already approved persistent effect indications listed above. Three studies were conducted to provide substantial evidence for these indications.

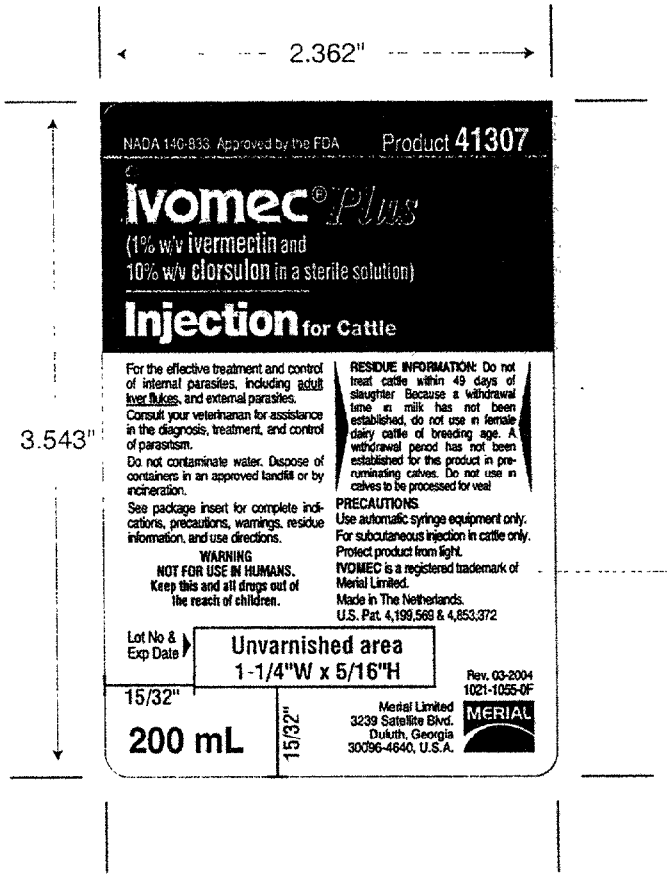
No patent information was submitted with this application.

6. ATTACHMENTS

Facsimile Labeling is attached as indicated below:

A. 50, 200, and 500 mL – container label and box carton
B. 1000 mL – base label and outsert
C. Package insert for 50, 200, and 500 mL container sizes


3.543'
1.732"
7/32"
Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.
Do not contaminate water. Dispose of containers in an approved landfill or by incineration.
See package insert for complete indications, precautions, warnings, residue information, and use directions
WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.
Lot No & Exp Date
Unvarnished area
1-1/4"W x 5/16"H
1021-1050-0F
Rev 03-2004
NADA 140-813
Approved by the FDA Product 41306
Ivomec Plus
(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)
Injection for Cattle
For the effective treatment and control of internal parasites, including adult liver flukes, and external parasites
50 mL
MERIAL
RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.
PRECAUTIONS
For subcutaneous injection in cattle only
Protect product from light.
IVOMEC is a registered trademark of Merial Limited.
Made in The Netherlands.
U.S. Pat. 4,199,569 & 4,853,372
Merial Limited, Duluth, Georgia, U.S.A


2.362"
3.543"
NADA 140-833, Approved by the FDA
Product 41307
Ivomec® Plus
(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)
Injection for Cattle
For the effective treatment and control of internal parasites, including adult liver flukes, and external parasites.
Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.
Do not contaminate water. Dispose of containers in an approved landfill or by incineration.
See package insert for complete indications, precautions, warnings, residue information, and use directions.
WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.
RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.
PRECAUTIONS
Use automatic syringe equipment only.
For subcutaneous injection in cattle only.
Protect product from light.
IVOMEC is a registered trademark of Merial Limited.
Made in The Netherlands.
U.S. Pat. 4,199,569 & 4,853,372
Lot No & Exp Date
Unvarnished area
1-1/4"W x 5/16"H
Rev. 03-2004
1021-1055-0F
15/32"
200 mL
15/32"
Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U.S.A.
MERIAL

3.937"

3.937"

NADA 140-833, Approved by the FDA

Product **41308**

Ivomec® *Plus*

(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)

Injection for Cattle

For the effective treatment and control of internal parasites, including adult liver flukes, and external parasites.

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

Do not contaminate water. Dispose of containers in an approved landfill or by incineration.

See package insert for complete indications, precautions, warnings, residue information, and use directions.

WARNING

NOT FOR USE IN HUMANS.

Keep this and all drugs out of the reach of children.

RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal

PRECAUTIONS

Use automatic syringe equipment only.

For subcutaneous injection in cattle only.

Protect product from light.

IVOMEC is a registered trademark of Merial Limited

Made in The Netherlands.

U.S. Pat. 4,199,569 & 4,853,372

Lot No & Exp Date

Unvarnished area
1-1/4"W x 5/16"H

9/16"

1/2"

500 mL

Rev. 03-2004
1021-1059-0F

Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U.S.A.

MERIAL

31¼"

13"

1050105201

NADA 140-833, Approved by the FDA

Ivomec® Plus

(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)

Injection for Cattle

For the effective treatment and control of internal parasites, including adult liver flukes, and external parasites.

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

INTRODUCTION

The ability of IVOMEC® (ivermectin) to deliver internal and external parasite control has been proven in cattle markets around the world. Now, Merial Limited combines ivermectin, the active ingredient of IVOMEC, with clorsulon, an effective adult flukicide.

A single injection of IVOMEC Plus (ivermectin and clorsulon) offers all the benefits of IVOMEC plus control of adult *Fasciola hepatica.*

The dosage level of clorsulon supplied by IVOMEC Plus is effective only against adult liver flukes *(Fasciola hepatica).*

PRODUCT DESCRIPTION

IVOMEC Plus is a ready-to-use sterile solution containing 1% w/v ivermectin, 10% clorsulon, 40% glycerol formal, and propylene glycol, q.s. ad 100%. It is formulated to deliver the recommended dose level of 200 mcg ivermectin/kg and 2 mg clorsulon/kg given subcutaneously behind the shoulder at the rate of 1 mL per 110 lb (50 kg) body weight.

MODE OF ACTION

Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Clorsulon is rapidly absorbed into the circulating blood. Erythrocytes with bound drug as well as plasma are ingested by *Fasciola hepatica.* Adult *Fasciola hepatica* are killed by clorsulon because of inhibition of enzymes in the glycolytic pathway, which is their primary source of energy.

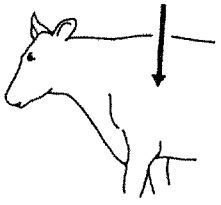
INDICATIONS

IVOMEC Plus Injection is indicated for the effective treatment and control of the following parasites of cattle:

Gastrointestinal Roundworms (adults and fourth-stage larvae):
Ostertagia ostertagi (including inhibited *O. ostertagi*)
O. lyrata
Haemonchus placei
Trichostrongylus axei
T. colubriformis
Cooperia oncophora
C. punctata
C. pectinata
Bunostomum phlebotomum
Nematodirus helvetianus (adults only)
N. spathiger (adults only)
Oesophagostomum radiatum
Lungworm (adults and fourth-stage larvae):

ADMINISTRATION

IVOMEC® Plus (ivermectin and clorsulon) Injection is to be given subcutaneously only. Animals should be appropriately restrained to achieve the proper route of administration. Use of a 16-gauge, 1/2" to 3/4" sterile needle is recommended. Inject the solution subcutaneously (under the skin) behind the shoulder (see illustration).



Any single-dose syringe or standard automatic syringe equipment may be used with the 50 mL pack size. When using the 200 mL, 500 mL or 1000 mL pack size, use only automatic syringe equipment.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infections.

No special handling or protective clothing is necessary.

The viscosity of the product increases in cool temperatures. Administering IVOMEC Plus at temperatures of 5°C (41°F) or below may be difficult. Users can make dosing easier by warming both the product and injection equipment to about 15°C (59°F).

ANIMAL SAFETY

In breeding animals (bulls and cows), ivermectin and clorsulon used at the recommended level had no effect on breeding performance.

WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Merial at 1-888-637-4251.

RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

Transitory discomfort has been observed in some cattle following subcutaneous administration. Soft-tissue swelling at the injection site has also been observed. These reactions have disappeared without treatment. Divide doses greater than 10 mL between two injection sites to reduce occasional discomfort or site reaction. Different injection sites should be used for other parenteral products.

IVOMEC Plus Injection has been developed specifically for use in cattle **only.** This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

For subcutaneous injection in cattle only.

This product is not for intravenous or intramuscular use.

When to Treat Cattle with Grubs

IVOMEC Plus effectively controls all stages of cattle grubs. However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble fly) season.

Destruction of *Hypoderma larvae* (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions including the possibility of fatalities. Killing *Hypoderma lineatum* when it is in the tissue surrounding the esophagus (gullet) may cause bloat; killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. These reactions are not specific to treatment with IVOMEC Plus, but can occur with any successful treatment of grubs. Cattle should be treated either before or after stages of grub development. Consult your veterinarian concerning the proper time for treatment.

Dictyocaulus viviparus

Liver Flukes:
Fasciola hepatica (adults only)

Cattle Grubs (parasitic stages):
Hypoderma bovis
H. lineatum

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites (cattle scab*):
Psoroptes ovis (syn. *P. communis* var. *bovis*)
Sarcoptes scabiei var. *bovis*

Persistent Activity
IVOMEC Plus Injection has been proved to effectively control infections and to protect cattle from reinfection with *Dictyocaulus viviparus* and *Oesophagostomum radiatum* for 28 days after treatment; *Ostertagia ostertagi*, *Trichostrongylus axei* and *Cooperia punctata* for 21 days after treatment; *Haemonchus placei*, and *Cooperia oncophora* for 14 days after treatment.

*Ivermectin has been approved as a scabicide by USDA/APHIS. Federal regulations require that cattle infested with or exposed to scabies (i.e., infestations with *Psoroptes ovis*) be treated. Ivermectin when used according to label instructions meets this requirement. Treated cattle may be shipped interstate, but they must not be mixed with other cattle for 14 days following treatment. The federal regulations make no restriction on the movement of cattle not affected with or exposed to scabies. However, individual states have additional regulations to govern the interstate shipment of cattle and the regulatory veterinarian in the state of destination should be consulted for applicable regulations on the use of ivermectin in the control of scabies.

DOSAGE
IVOMEC Plus should be given only by subcutaneous injection at a dose volume of 1 mL per 110 lb (50 kg) body weight. This volume will deliver 10 mg ivermectin and 100 mg clorsulon. For example:

Body Weight (lb)	Dose (mL)
220	2
330	3
440	4
550	5
660	6
770	7
880	8
990	9
1100	10

Cattle treated with IVOMEC Plus after the end of the heel fly season may be retreated with ivermectin during the winter for internal parasites, mange mites or sucking lice, without danger of grub-related reactions. A planned parasite control program is recommended.

Protect product from light.

Environmental Safety
Studies indicate that when ivermectin comes in contact with soil it readily and tightly binds to the soil and becomes inactive overtime. Free ivermectin may adversely affect fish and certain aquatic organisms. Do not permit water runoff from feedlots to enter lakes, streams or ponds. Do not contaminate water by direct application or by improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

As with other avermectins, ivermectin is excreted in the dung of treated animals and can inhibit the reproduction and growth of pest and beneficial insects that use dung as a source of food and for reproduction. The magnitude and duration of such effects are species and life-cycle specific. When used according to label directions, the product is not expected to have an adverse impact on populations of dung-dependent insects.

HOW SUPPLIED
IVOMEC Plus Injection is available in five ready-to-use pack sizes:

The 50 mL pack is a multiple-dose, rubber-capped bottle. Each bottle contains sufficient solution to treat 10 head of 550 lb (250 kg) cattle.

The 200 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 40 head of 550 lb (250 kg) cattle.

The 500 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 100 head of 550 lb (250 kg) cattle.

The 2 x 500 mL pack includes two 500 mL packs with sufficient solution to treat 200 head of 550 lb (250 kg) cattle.

The 1000 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 200 head of 550 lb (250 kg) cattle.

Merial Limited, a company limited by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex CM19 5TG, England, and domesticated in Delaware, USA as Merial LLC.

Made in The Netherlands.

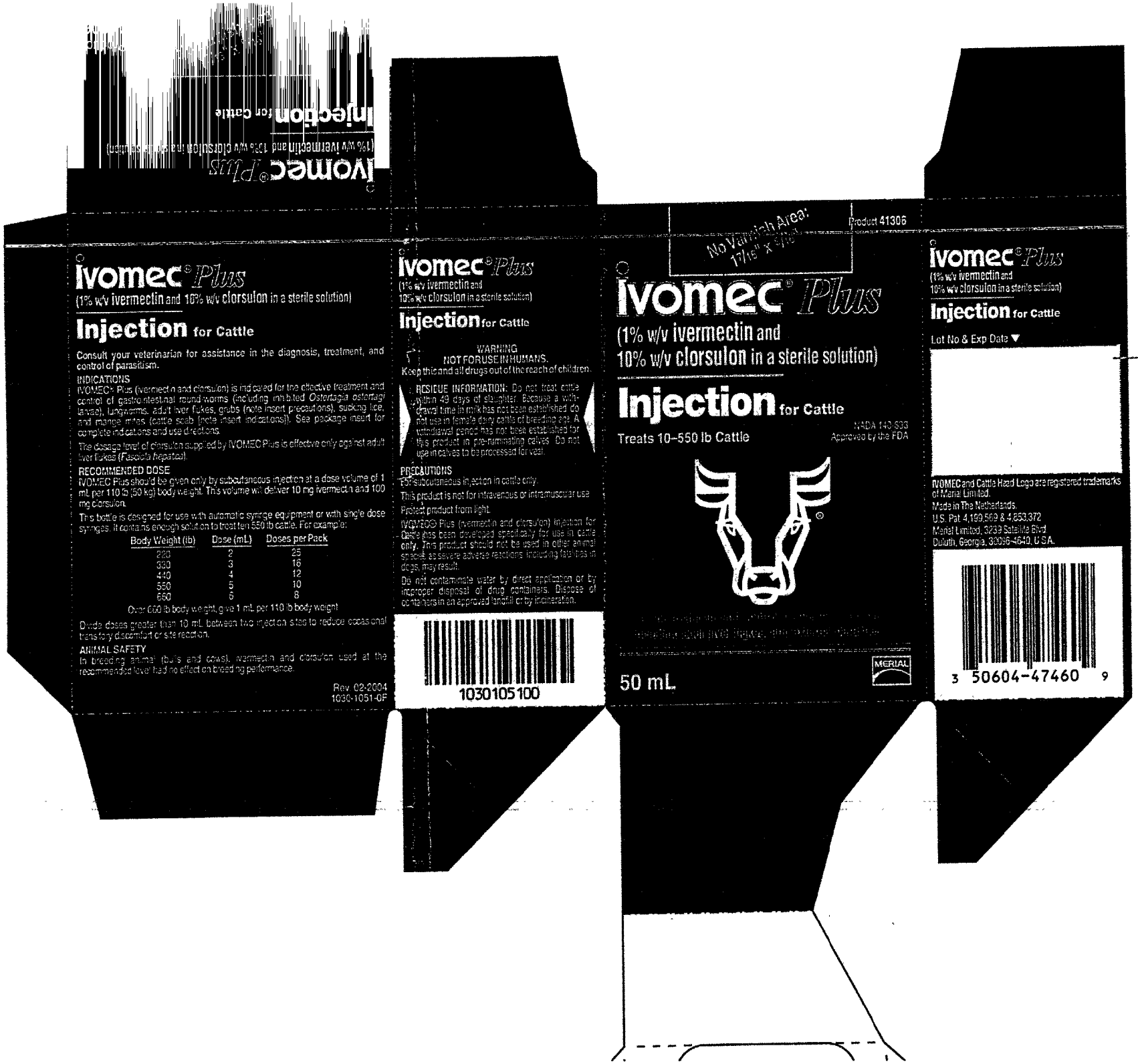
U.S. Pat. 4,199,569 & 4,853,372

Rev. 02-2004
1050-1052-01F2

Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U.S.A.

Front

Back



No Varnish Area
1½" x 1"
(also white)

Product 41307

Ivomec® Plus

(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)

Injection for Cattle

Treats 40–550 lb Cattle

NADA 140-833
Approved by the FDA

For the treatment and control of internal parasites, including adult liver flukes, and external parasites.

200 mL

MERIAL

Ivomec® Plus
(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)
Injection for Cattle

Lot No & Exp Date

No Varnish Area:
1½" x 1"
(also white)

IVOMEC® Plus (ivermectin and clorsulon) combines ivermectin for internal and external parasite control and clorsulon, which effectively controls adult liver flukes.

Made in The Netherlands.

U.S. Pat. 4,199,569 & 4,853,372

Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U.S.A.

3 50604-47471 5

Ivomec® Plus
(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)
Injection for Cattle
200 mL
Product 41307

Ivomec® Plus

(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)

Injection for Cattle

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

INDICATIONS

IVOMEC® Plus (ivermectin and clorsulon) is indicated for the effective treatment and control of gastrointestinal round-worms (including inhibited *Ostertagia ostertagi* larvae), lungworms, adult liver flukes, grubs (note insert precautions), sucking lice, and mange mites (cattle scab [note insert indications]). See package insert for complete indications and use directions.

The dosage level of clorsulon supplied by IVOMEC Plus is effective only against adult liver flukes (*Fasciola hepatica*).

RECOMMENDED DOSE

IVOMEC Plus should be given only by subcutaneous injection at a dose volume of 1 mL per 110 lb (50 kg) body weight. This volume will deliver 10 mg ivermectin and 100 mg clorsulon.

This bottle is designed for use with automatic syringe equipment only. It contains enough solution to treat ten 550 lb cattle. For example:

Body Weight (lb)	Dose (mL)	Doses per Pack
220	2	100
330	3	66
440	4	50
550	5	40
660	6	33
770	7	28
880	8	25
990	9	22
1100	10	20

Divide doses greater than 10 mL between two injection sites to reduce occasional transitory discomfort or site reaction.

Rev. 02-2004
1030-1056-0F

Ivomec® Plus
(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)
Injection for Cattle

ANIMAL SAFETY

In breeding animal (bulls and cows), ivermectin and clorsulon used at the recommended level had no effect on breeding performance.

WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.

RESIDUE INFORMATION:
Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

Use automatic syringe equipment only.

For subcutaneous injection in cattle only.

This product is not for intravenous or intramuscular use.

Protect product from light.

IVOMEC® Plus (ivermectin and clorsulon) Injection for Cattle has been developed specifically for use in cattle only. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

Do not contaminate water by direct application or by improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

1030105600

Product 41308

Ivomec® Plus

(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)

Injection for Cattle

Treats 100–550 lb Cattle

NADA 140-833
Approved by the FDA

For the treatment and control of internal parasites, including adult liver flukes, and external parasites

500 mL

MERIAL

Ivomec® Plus
(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)
Injection for Cattle

Lot No & Exp Date ▼

Varnish Area:
2" x 1"
(so white)

IVOMEC® Plus (ivermectin and clorsulon) combines ivermectin for internal and external parasite control and clorsulon, which effectively controls adult liver flukes.

Made in The Netherlands.

U.S. Pat. 4,199,569 & 4,853,372

Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U.S.A.

3 50604-47472 2

500 mL

No Varnish Area:
1½" x 3½"

Product
41308

Ivomec® Plus

(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)

Injection for Cattle

Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

INDICATIONS

IVOMEC® Plus (ivermectin and clorsulon) is indicated for the effective treatment and control of gastrointestinal round-worms (including inhibited *Ostertagia ostertagi* larvae), lungworms, adult liver flukes, grubs (note insert precautions), sucking lice, and mange mites (cattle scab [note insert indications]). See package insert for complete indications and use directions.

The dosage level of clorsulon supplied by IVOMEC Plus is effective only against adult liver flukes (*Fasciola hepatica*).

RECOMMENDED DOSE

IVOMEC Plus should be given only by subcutaneous injection at a dose volume of 1 mL per 110 lb (50 kg) body weight. This volume will deliver 10 mg ivermectin and 100 mg clorsulon.

This bottle is designed for use with automatic syringe equipment only. It contains enough solution to treat one hundred 550 lb cattle. For example:

Body Weight (lb)	Dose (mL)	Doses per Pack
220	2	250
330	3	166
440	4	125
550	5	100
660	6	83
770	7	71
880	8	62

Divide doses greater than 10 mL between two injection sites to reduce occasional transitory discomfort or site reaction.

Rev. 02-2004
1030-1051-0F

Ivomec® Plus

(1% w/v ivermectin and 10% w/v clorsulon in a sterile solution)

Injection for Cattle

ANIMAL SAFETY

In breeding animals (bulls and cows), ivermectin and clorsulon used at the recommended level had no effect on breeding performance.

WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.

RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

Use automatic syringe equipment only.

For subcutaneous injection in cattle only.

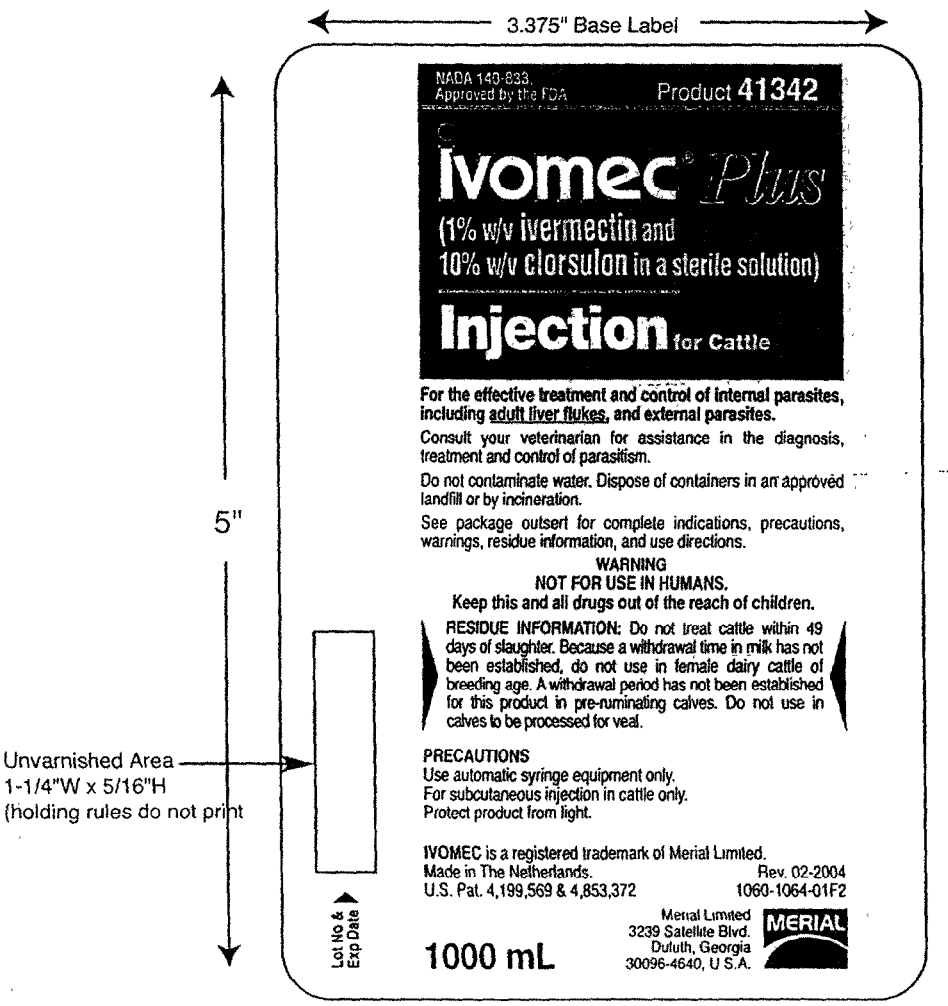
This product is not for intravenous or intramuscular use.

Protect product from light.

IVOMEC® Plus (ivermectin and clorsulon) Injection for Cattle has been developed specifically for use in cattle **only**. This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

Do not contaminate water by direct application or by improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

1030106100


3.375" Base Label
5"
Unvarnished Area
1-1/4"W x 5/16"H
(holding rules do not print
NADA 140-833,
Approved by the FDA
Product 41342
Ivomec® Plus
(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)
Injection for Cattle
For the effective treatment and control of internal parasites, including adult liver flukes, and external parasites.
Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.
Do not contaminate water. Dispose of containers in an approved landfill or by incineration.
See package outsert for complete indications, precautions, warnings, residue information, and use directions.
WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.
RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.
PRECAUTIONS
Use automatic syringe equipment only.
For subcutaneous injection in cattle only.
Protect product from light.
IVOMEC is a registered trademark of Merial Limited.
Made in The Netherlands.
U.S. Pat. 4,199,569 & 4,853,372
Rev. 02-2004
1060-1064-01F2
Lot No & Exp Date
1000 mL
Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U S.A.
MERIAL

0078

2.524" Panel 1 | 2.462" Panel 2 | 2.403" Panel 3 | 2.292" Panel 4

016"

Ivomec® Plus

(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)

Injection for Cattle

For the effective treatment and control of internal parasites, including adult liver flukes, and external parasites.

INTRODUCTION

The ability of IVOMEC® (ivermectin) to deliver internal and external parasite control has been proven in cattle markets around the world. Now, Merial Limited combines ivermectin, the active ingredient of IVOMEC, with clorsulon, an effective adult flukicide.

A single injection of IVOMEC Plus (ivermectin and clorsulon) offers all the benefits of IVOMEC plus control of adult *Fasciola hepatica.*

The dosage level of clorsulon supplied by IVOMEC Plus is effective only against adult liver flukes *(Fasciola hepatica).*

PRODUCT DESCRIPTION

IVOMEC Plus is a ready-to-use sterile solution containing 1% w/v ivermectin, 10% clorsulon, 40% glycerol formal, and propylene glycol, q.s. ad 100%. It is formulated to deliver the recommended dose level of 200 mcg ivermectin/kg and 2 mg clorsulon/kg given subcutaneously behind the shoulder at the rate of 1 mL per 110 lb (50 kg) body weight.

MODE OF ACTION

Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels and they do not readily cross the blood-brain barrier.

Clorsulon is rapidly absorbed into the circulating blood. Erythrocytes with bound drug as well as plasma are ingested by *Fasciola hepatica.* Adult *Fasciola hepatica* are killed by clorsulon because of inhibition of enzymes in the glycolytic pathway, which is their primary source of energy.

INDICATIONS

IVOMEC Plus Injection is indicated for the effective treatment and control of the following parasites of cattle:

Gastrointestinal Roundworms (adults and fourth-stage larvae):
Ostertagia ostertagi (including inhibited *O. ostertagi*)
O. lyrata
Haemonchus placei
Trichostrongylus axei
T. colubriformis
Cooperia oncophora
C. punctata
C. pectinata
Bunostomum phlebotomum
Nematodirus helvetianus (adults only)
N. spathiger (adults only)
Oesophagostomum radiatum

Lungworms (adults and fourth-stage larvae):
Dictyocaulus viviparus

Liver Flukes:
Fasciola hepatica (adults only)

Cattle Grubs (parasitic stages):
Hypoderma bovis
H. lineatum

Sucking Lice:
Linognathus vituli
Haematopinus eurysternus
Solenopotes capillatus

Mange Mites (cattle scab*):
Psoroptes ovis (syn. *P. communis* var. *bovis*)
Sarcoptes scabiei var. *bovis*

Persistent Activity

IVOMEC Plus Injection has been proved to effectively control infections and to protect cattle from reinfection with *Dictyocaulus viviparus* and *Oesophagostomum radiatum* for 28 days after treatment; *Ostertagia ostertagi, Trichostrongylus axei* and *Cooperia punctata* for 21 days after treatment; *Haemonchus placei,* and *Cooperia oncophora* for 14 days after treatment.

*Ivermectin has been approved as a scabicide by USDA/APHIS. Federal regulations require that cattle infested with or exposed to scabies (i.e., infestations with *Psoroptes ovis*) be treated. Ivermectin when used according to label instructions meets this requirement. Treated cattle may be shipped interstate, but they must not be mixed with other cattle for 14 days following treatment. The federal regulations make no restriction on the movement of cattle not affected with or exposed to scabies. However, individual states have additional regulations to govern the interstate shipment of cattle and the regulatory veterinarian in the state of destination should be consulted for applicable regulations on the use of ivermectin in the control of scabies.

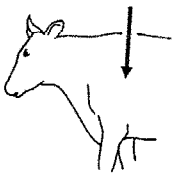
DOSAGE

IVOMEC Plus should be given only by subcutaneous injection at a dose volume of 1 mL per 110 lb (50 kg) body weight. This volume will deliver 10 mg ivermectin and 100 mg clorsulon. For example:

Body Weight (lb)	Dose (mL)
220	2
330	3
440	4
550	5
660	6
770	7
880	8
990	9
1100	10

ADMINISTRATION

IVOMEC Plus (ivermectin and clorsulon) Injection is to be given subcutaneously only. Animals should be appropriately restrained to achieve the proper route of administration. Use of a 16-gauge, 1/2" to 3/4" sterile needle is recommended. Inject the solution subcutaneously (under the skin) behind the shoulder (see illustration).



Any single-dose syringe or standard automatic syringe equipment may be used with the 50 mL pack size. When using the 200 mL, 500 mL or 1000 mL pack size, use only automatic syringe equipment.

Use sterile equipment and sanitize the injection site by applying a suitable disinfectant. Clean, properly disinfected needles should be used to reduce the potential for injection site infections.

No special handling or protective clothing is necessary.

The viscosity of the product increases in cool temperatures. Administering IVOMEC Plus at temperatures of 5°C (41°F) or below may be difficult. Users can make dosing easier by warming both the product and injection equipment to about 15°C (59°F).

ANIMAL SAFETY

In breeding animals (bulls and cows), ivermectin and clorsulon used at the recommended level had no effect on breeding performance.

WARNING
NOT FOR USE IN HUMANS.
Keep this and all drugs out of the reach of children.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Merial at 1-888-637-4251.

RESIDUE INFORMATION: Do not treat cattle within 49 days of slaughter. Because a withdrawal time in milk has not been established, do not use in female dairy cattle of breeding age. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

Transitory discomfort has been observed in some cattle following subcutaneous administration. Soft-tissue swelling at the injection site has also been observed. These reactions have disappeared without treatment. Divide doses greater than 10 mL between two injection sites to reduce occasional discomfort or site reaction. Different injection sites should be used for other parenteral products.

IVOMEC® Plus Injection has been developed specifically for use in cattle **only.** This product should not be used in other animal species as severe adverse reactions, including fatalities in dogs, may result.

For subcutaneous injection in cattle **only.**

This product is not for intravenous or intramuscular use.

When to Treat Cattle with Grubs

IVOMEC Plus effectively controls all stages of cattle grubs. However, proper timing of treatment is important. For most effective results, cattle should be treated as soon as possible after the end of the heel fly (warble fly) season.

Destruction of *Hypoderma larvae* (cattle grubs) at the period when these grubs are in vital areas may cause undesirable host-parasite reactions including the possibility of fatalities. Killing *Hypoderma lineatum* when it is in the tissue surrounding the esophagus (gullet) may cause bloat; killing *H. bovis* when it is in the vertebral canal may cause staggering or paralysis. These reactions are not specific to treatment with IVOMEC Plus, but can occur with any successful treatment of grubs. Cattle should be treated either before or after stages of grub development. Consult your veterinarian concerning the proper time for treatment.

Cattle treated with IVOMEC Plus after the end of the heel fly season may be retreated with ivermectin during the winter for internal parasites, mange mites or sucking lice, without danger of grub-related reactions. A planned parasite control program is recommended.

Protect product from light.

Environmental Safety

Studies indicate that when ivermectin comes in contact with soil it readily and tightly binds to the soil and becomes inactive overtime. Free ivermectin may adversely affect fish and certain aquatic organisms. Do not permit water runoff from feedlots to enter lakes, streams, or ponds. Do not contaminate water by direct application or by improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

As with other avermectins, ivermectin is excreted in the dung of treated animals and can inhibit the reproduction and growth of pest and beneficial insects that use dung as a source of food and for reproduction. The magnitude and duration of such effects are species and life-cycle specific. When used according to label directions, the product is not expected to have an adverse impact on populations of dung-dependent insects.

HOW SUPPLIED

IVOMEC Plus Injection is available in five ready-to-use pack sizes:

The 50 mL pack is a multiple-dose, rubber-capped bottle. Each bottle contains sufficient solution to treat 10 head of 550 lb (250 kg) cattle.

The 200 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 40 head of 550 lb (250 kg) cattle.

The 500 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 100 head of 550 lb (250 kg) cattle.

The 2 x 500 mL pack includes two 500 mL packs with sufficient solution to treat 200 head of 550 lb (250 kg) cattle.

The 1000 mL pack is a soft, collapsible pack designed for use with automatic syringe equipment. Each pack contains sufficient solution to treat 200 head of 550 lb (250 kg) cattle.

Merial Limited, a company limited by shares registered in England and Wales (registered number 3332751) with a registered office at PO Box 327, Sandringham House, Sandringham Avenue, Harlow Business Park, Harlow, Essex CM19 5TG, England, and domesticated in Delaware, USA as Merial LLC.

Made in The Netherlands.

Merial Limited
3239 Satellite Blvd.
Duluth, Georgia
30096-4640, U.S.A.

U.S. Pat. 4,199,569 & 4,853,372

Rev. 02-2004

NADA 140-633,
Approved by the FDA

Product 41342

Ivomec® Plus

(1% w/v ivermectin and
10% w/v clorsulon in a sterile solution)

Injection for Cattle

Do not contaminate water by direct application or by improper disposal of drug containers. Dispose of containers in an approved landfill or by incineration.

Consult your veterinarian for assistance in the diagnosis, treatment and control of parasitism.

1060-1064-01F2

1000 mL

MERIAL

16"

2.292" Panel 5 — 2.403" Panel 6 — 2.462" Panel 7 — 2.524" Front Panel